REMARKS

Applicants have received and reviewed the Office Action dated August 28, 2009.

By way of response, Applicants have cancelled claim 33 without prejudice. Applicants reserve the right to pursue the subject matter of these claims in one or more continuation applications.

Claims 1-4, 9-10, 17, 20 have been amended. Applicants submit that amendments are supported throughout the specification including at page 9, line 15 to page 10, line 2; page 13, lines 6-16; page 12, lines 1-5; page 5, lines 22-26 ; and page 13, lines 17-21 of the specification as originally filed.

35 U.S.C. § 102(e)

Claims 1, 9, 11-17, 19-22, 25, 28-31 and 33 were rejected under 35 U.S.C. 102(e) over Handy et al., US 6,997,863. Claim 33 has been cancelled rendering the rejection of this claim moot. Applicants traverse the rejection with respect to the remainder of the claims.

"Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." Lindemann Mashinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984); See also, MPEP §2131. Applicants submit that cited reference does not disclose all of the elements of the rejected claims.

The cited document teaches a treatment method based on administration of a plurality of single domain nanomagnetic particles with a coating attached to a ligand designed to target a specific site in a patient. See col. 6 lines 61 to col 7, line 3.That is, the administered particles are not microparticles containing many nanomagnets fixed in a matrix, but merely the individual nanomagnets each associated with a targeting ligand. These particles are designed to attach to and be internalized by cancer cells. Furthermore, Handy does not mention SAR or VAR or measurements of specific heat output or how heating might be affected by particle characteristics. Therefore, the cited document does not disclose all of the elements of the claims.

Based on the foregoing, Applicants request withdrawal of this rejection.

Claims 1-4, 9, 11-22, 25 and 33 were rejected under 35 U.S.C. 102(e) over Chatterjee et al., US 2004/0065969. Claim 33 has been cancelled rendering the rejection of this claim moot. Applicants traverse the rejection with respect to the remainder of the claims.

"Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." Lindemann Mashinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984); See also, MPEP §2131. Applicants submit that cited reference does not disclose all of the elements of the rejected claims.

Chatterjee describes methods for microencapsulation of an agent where the agent could be magnetic nanoparticles of size 5 to 50 nm. Up to 40% of the weight of the microparticle could be the 'agent' and the microparticle can be up to 1000 nm in size. These particles can be manipulated by magnetic fields, i.e. used for separation from a fluid medium. There is no teaching of using these particles for hyperthermia, no mention of specifically addressing any of the problems associated with trying to maximize heating, no discussion of measurements of SAR or VAR and no mention of the need to disperse the particles throughout the matrix to avoid aggregation. Thus, the cited reference does not disclose all of the elements of the claims.

Based on the foregoing, Applicants request withdrawal of this rejection.

35 U.S.C. § 102(b)

Claims 1-3, 9, 11-22, 25, 28, 29 and 33 were rejected under 35 U.S.C. 102(b) over Pouliquen, 2001. Claim 33 has been cancelled rendering the rejection of this claim moot. Applicants traverse the rejection with respect to the remainder of the claims.

"Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." Lindemann Mashinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984); See also, MPEP §2131. Applicants submit that cited reference does not disclose all of the elements of the rejected claims.

Pouliquen (2001) teaches magnetite dextran nanocapsules (MDN) and relaxivity of nanocapsules. The review discusses the clustering of super-paramagnetic particles into a high density composite. However, it does not teach the microparticle composition or method of use

of the present application. The technical implications of the particular values of SAR, VAR and W/g relate to the dynamic magnetic properties of claimed compositions and such values are not taught or suggested by the cited reference.

Applicants wish to draw to the Examiner's attention that the magnetic characteristics of nanomagnetic particles are notoriously sensitive to variations in any number of parameters and are not just purely determined by their chemical composition. For example, nanomagnetic particles in the size range of less than 50 nm are only made up of a relatively small number of atoms and so they behave very differently than much larger particles or bulk samples of the same material. This is especially the case when considering the dynamic magnetic characteristics of the particles - that is, how they respond in a time varying magnetic field. In instances where only the static or DC magnetic characteristics are important these sensitivities are far less important.

Parameters such as average particle size and size distribution impact the ability of the claimed microparticles to be used in hyperthermia; surface characteristics and interaction effects between neighboring particles all combine together to determine how much heat (i.e. the SAR, VAR or W/g) is produced under specified magnetic field conditions of frequency and strength. The microparticle composition as presently claimed, achieves useful levels of VAR or W/g. It can only be done by considering the whole microparticle construct, that is, the nanomagnetic particles embedded in a polymer matrix, as a whole. Indeed, the applicant is of the opinion that none of the microparticles systems disclosed in the cited literature could achieve the levels of VAR as currently claimed and subject to the same magnetic field conditions because the microparticles of the cited document were never designed for such a purpose. As such, it would be extremely unlikely for the microparticles of the cited document to achieve useful VARs purely by accident.

In addition, it is very important to consider the completely destructive effects of particle aggregation. Nanoparticles, by virtue of their size, have an extreme tendency to aggregate into clumps. Aggregation is an extreme case of particle interaction and, in the applicant's experience, will completely destroy the individual nanoparticles ability to heat under clinically acceptable magnetic field conditions, although they can be made to heat if there are no restrictions on the magnetic field. Again, most normal applications (e.g. MRI contrast agents, cell separation

systems etc) will not be too adversely effected by particle aggregation. In the composition as claimed, the magnetic nanoparticles disperse throughout the polymer matrix and do not form aggregated clumps within the matrix. A higher concentration of nanoparticles within each microsphere is needed in order to obtain the required VAR (i.e. it would be quite easy to put one or two nanoparticles into each microsphere and not have them aggregate but this would not provide enough VAR). We refer the examiner to the need for dispersion in lines 15 to 23 on page 9, and Example 4 of the specification as originally filed.

Based on the foregoing, Applicants request withdrawal of the rejection.

Claims 1-4, 9, 11-17, 19-22, 25 and 33 were rejected under 35 U.S.C. 102(b) over Widder et al., US 4,247,406. Claim 33 has been cancelled rendering the rejection of this claim moot. Applicants traverse the rejection with respect to the remainder of the claims.

"Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." Lindemann Mashinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 1458 (Fed. Cir. 1984); See also, MPEP §2131. Applicants submit that cited reference does not disclose all of the elements of the rejected claims.

Widder describes microspheres with average size less than 1.5 micron with magnetic particles embedded therein. These microspheres are designed to be magnetically localizable. That is, they can be maneuvered into a desired position within a patient by judicious use of externally applied magnetic fields. The microspheres are formed from a biodegradable amino acid polymer matrix.

Again, there is no teaching or suggestion for the use of these particles in hyperthermia treatment, no mention of specifically addressing any of the problems associated with trying to maximize heating, or any disclosure of the measurements of SAR or VAR; and no mention of the need to disperse the particles throughout the matrix to avoid aggregation. The present invention is not concerned with the biodegradability of the compositions, in fact the composition of the present application preferably is <u>not</u> biodegradable. The document is not concerned with the use of a composition in hyperthermia treatment and as such, does not consider the properties

required for use in hyperthermia treatment or the safety concerns associated with using such a compounds.

Nanoparticles, by virtue of their size, have an extreme tendency to aggregate into clumps. Aggregation is an extreme case of particle interaction and, in the applicant's experience, will completely destroy the individual nanoparticles ability to heat under clinically acceptable magnetic field conditions, although they can be made to heat if there are no restrictions on the magnetic field. Again, most normal applications (e.g. MRI contrast agents, cell separation systems etc) will not be too adversely effected by particle aggregation. In the composition as claimed, the magnetic nanoparticles disperse throughout the polymer matrix and do not form aggregated clumps within the matrix. A higher concentration of nanoparticles within each microsphere is needed in order to obtain the required VAR (i.e. it would be quite easy to put one or two nanoparticles into each microsphere and not have them aggregate but this would not provide enough VAR). We refer the examiner to the need for dispersion in lines 15 to 23 on page 9, and Example 4 of the specification as originally filed.

Applicants submit that the cited document does not teach the composition of the present claims. Applicants request withdrawal of the rejection on this basis.

35 U.S.C. § 103(a)

Claims 1-4, 8-22, 25, 28-31 and 33 were rejected under 35 U.S.C. 103(a) over Gray et al, US 6,167,313 in view of Lesniak et al., US 6,541,039 and Handy et al., US 6,997,863. Claim 33 has been cancelled rendering the rejection of this claim moot. Applicants traverse the rejection with respect to the rest of the claims.

The examiner concedes that Gray does not teach the magnetic material in the form of nanoparticles. As discussed above, the use of nanoparticles is different than other types of particles. Nanoparticles, by virtue of their size, have an extreme tendency to aggregate into clumps. Aggregation is an extreme case of particle interaction and, in the applicant's experience, will completely destroy the individual nanoparticles ability to heat under clinically acceptable magnetic field conditions, although they can be made to heat if there are no restrictions on the magnetic field. Again, most normal applications (e.g. MRI contrast agents, cell separation systems etc) will not be too adversely effected by particle aggregation. In the composition as

claimed, the magnetic nanoparticles disperse throughout the polymer matrix and do not form aggregated clumps within the matrix. A higher concentration of nanoparticles within each microsphere is needed in order to obtain the required VAR (i.e. it would be quite easy to put one or two nanoparticles into each microsphere and not have them aggregate but this would not provide enough VAR). We refer the examiner to the need for dispersion in lines 15 to 23 on page 9, and Example 4 of the specification as originally filed.

However, the examiner states that Lesniak discloses nanoscale particle which would be suited for use in tumor therapy by hyperthermia. Furthermore, the examiner has cited Handy as disclosing therapeutic methods for treatment of disease involving administration of a thermo-therapeutic magnetic composition to a patient and applying an alternating magnetic field to heat the thermo-therapeutic magnetic composition.

Applicants submit that the nano-scale particles of Lesniak are not the same as those as claimed. Lesniak discloses nano-scale particles having an iron oxide containing core and at least two shells surrounding the core. In its exposed state, the inner shell is positively charged and biodegradable at a low rate. The outer shell is biodegradable at a higher rate and makes the nano-scale particle appear to have an overall neutral or negative charge. In contrast, the microparticles claimed in the present application do not comprise a core or outer layers. The compositions claimed in the present application comprise nanomagnetic particles distributed within a matrix. Lesniak neither teaches nor suggests this composition.

Although the particles of Lesniak may be subjected to an alternating magnetic field to heat the iron core, Lesniak does not teach or suggest the SAR, VAR or preferred magnetic field conditions claimed in the amended claims. Similarly, Lesniak does not provide any information regarding the density of the coated particles or the fractional loading of magnetic oxide within the particles. Further, the size range of the microparticles of the present invention is substantially different from that disclosed in Lesniak.

Furthermore, it would not be obvious for a person skilled in the art to arrive at the present invention when combining the disclosures of Gray and Handy. Handy is directed towards a method based on the administration of a plurality of single domain nanomagnetic particles attached to a ligand. However, the document neither teaches nor suggests the distribution of the

nanomagnetic particles within a matrix, the required VAR or SAR or the size or specific heating conditions.

Therefore, Applicants submit that all of the elements of the claims are not taught when the documents Gray, Handy and Lesniak are combined. Applicants request withdrawal of this rejection.

Claims 1-4, 8-22, 25, 28-31 and 33 were rejected under 35 U.S.C. 103(a) over Jones et al., 2001. Claim 33 has been cancelled rendering the rejection of this claim moot. Applicants traverse the rejection with respect to the rest of the claims.

The journal article by Jones et al., (2001) describes the use of microspheres formulated to contain non-superparamagnetic ferromagnetic particles, which are much larger than the nanomagnets used in the microparticles claimed in the present application. In fact this article serves to highlight the exact problem the inventors had to overcome by using nanomagnets. That is, when the field strength used in the experiments described is 40 kA/m (approx 500 Oe - see p 389) it is far greater than the 60 to 120 Oe claimed in the present application which is clinically acceptable. The ferromagnetic particles used in the reported experiments in rabbit kidneys would not produce useful heating at the clinically acceptable magnetic field levels. Thus Jones et al., (2001) highlights the problems associated with using targeted heating but does not provide any solution to the problem.

Combining the disclosure of the Jones article with the teachings of Lesniak and Handy would not arrive at the composition or method as claimed. As stated above, Lesniak relates to nano-scale particles having an iron oxide containing core and at least two shells surrounding the core. In its exposed state the inner shell is positively charged and biodegradable at a low rate. The outer shell is biodegradable at a higher rate and makes the nano-scale particle appear to have an overall neutral or negative charge. In contrast, the composition of the present invention comprises a plurality of superparamagnetic nanoparticles dispersed throughout a polymer matrix in a way that minimizes the likelihood of physical contact between the superparamagnetic particles. Lesniak does not consider the importance or relevance of the dispersion of nanomagnetic particles within a matrix. In this regard, Lesniak neither teaches nor discusses the

importance of dispersing the nanomagnetic particles within a matrix and as such adds nothing to the teaching of Jones et al.

Handy is directed towards a method of treatment based on the administration of a plurality of single domain nanomagnetic particles attached to a ligand and does not relate to a composition containing nanomagnetic particles distributed in a matrix. A person skilled in the art would not have considered combining these documents nor arrived at the composition or method of the present invention since the distribution of magnetic particles within a matrix and the properties associated with use in a clinical magnetic filed are not addressed in either Handy or Jones.

The size of the microspheres of the present invention is in the range of 100 nm to 200 microns and as such is much larger than those disclosed in Lesniak, Jones or Handy. Thus, neither Lesniak nor Handy adds anything to the disclosure of Jones and in fact teaches away from the size range presently claimed. Furthermore, there is no discussion of SAR, VAR or preferred magnetic field conditions in either of Jones, Lesniak or Handy. Similarly, there is no information provided regarding the density of the coated particles or the fractional loading of magnetic oxide within the particles.

The method used to target the nanoscale particles in Lesniak is to "accumulate in the region of the body a magnetic fluid comprising nanoscale particles suspended in a fluid medium ...". In the text the statement is made that the magnetic fluid should be injected punctually into the tissue. Their nanoscale particles are designed to be readily imported directly into the inside of the tumor cells. By contrast, the microparticle composition of the present invention is specifically designed to be delivered to the target site via intra-vascular infusion and thence to embolise the capillary beds supplying the target site. None of Jones, Lesniak or Handy teach or suggest this route of administration or the problems associated with achieving the desired result.

Based on the foregoing, Applicants request withdrawal of this rejection.

Summary

In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,
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